

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dosuk D. Lee et al.	Confirmation No.:	5068
Serial No.:	09/153,133	Art Unit:	1617
Filed:	September 15, 1998	Examiner:	Layla Soroush
Customer No.:	21559		

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Arlington, VA 22313-1450

DECLARATION OF DR. ALIASSGHAR N. TOFIGHI  
UNDER 37 C.F.R. § 1.132

I, ALIASSGHAR N. TOFIGHI, declare:

1. I am a distinguished research fellow at Etex Corporation, the assignee of United States Patent Application Serial No. 09/153,133. I received a Ph.D. in Material Science from the National Polytechnic Institute of Toulouse (France) in 1982, specializing in the field of material science. I have over 19 years of experience in the field of calcium phosphate chemistry and bone cement biomaterials.

2. I have read and understood the Office Action, dated September 23, 2009, and Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter "Gerhart"), which is cited by the Office therein. This Declaration is presented to overcome the rejection of claims 45, 46, 58, 59, 73, and 75-77 under 35 U.S.C. § 103(a) for obviousness based on Gerhart in combination with Relyveld (U.S. Patent No. 4,016,252; hereinafter "Relyveld").

3. I have compared characteristics of the Gerhart composition, including the hardening characteristics, with characteristics of a composition within the scope of the pending claims. The composition of present claims 45, 46, 58, 59, 73, and 75-77 hardens, unexpectedly, in an endothermic reaction to form a poorly crystalline apatitic calcium phosphate. The Gerhart composition does not exhibit these properties, nor does Gerhart teach or suggest a method for

making a composition having the characteristics of the composition of present claims 45, 46, 58, 59, 73, and 75-77.

4. The composition of present claims 45, 46, 58, 59, 73, and 75-77 includes a calcium phosphate component comprising an amorphous calcium phosphate or poorly crystalline apatitic (PCA) calcium phosphate and an antigen or vaccine component. The composition hardens to form a PCA calcium phosphate. It is the calcium phosphate component of the composition of present claims 45, 46, 58, 59, 73, and 75-77 that reacts to form a PCA calcium phosphate. The composition forms a poorly crystalline apatite due to rapid crystallization of a metastable phase. The hardening reaction releases carbonate ions, a fraction of which are incorporated into the apatite lattice, which gives rise to a nonstoichiometric poorly crystalline apatite rich in  $\text{HPO}_4^{2-}$ . The final product (poorly crystalline apatite) is characterized by low crystallinity and reactive non-apatitic environments at the surface of poorly crystalline apatite crystals.

5. In addition, the composition of present claims 45, 46, 58, 59, 73, and 75-77 hardens in an endothermic reaction. The endothermic nature of the hardening reaction occurs as a result of the fast hydrolysis of the amorphous phase of the calcium phosphate into poorly crystalline apatite. ACP hydrolysis produces  $\text{OH}^-$  and  $\text{HPO}_4^{2-}$  ions from the  $\text{PO}_4^{3-}$  groups in the following reaction:  $\text{PO}_4^{3-} + \text{H}_2\text{O} \rightarrow \text{HPO}_4^{2-} + \text{OH}^-$ . The setting reaction uses heat (e.g., body heat) to begin and develop, which is an unexpected property of the calcium phosphate composition of present claims 45, 46, 58, 59, 73, and 75-77. The endothermic nature of the reaction that produces the composition of present claims 45, 46, 58, 59, 73, and 75-77 allows the reaction progress to be controlled by regulating the amount of heat available to support the reaction. The composition components react minimally at room temperature and below, but harden in about 30 minutes once exposed to body temperature.

6. In contrast, the Gerhart composition is a "polymer matrix [that] serves as a supporting binder for particles of biocompatible inorganic salts and ceramics" (col. 2, lines 34-36). The curing reaction in the Gerhart composition involves the polymerization of a biodegradable polyester with a chemical cross-linking agent to form a solidified cement matrix (see col. 5, lines 25-27). It is the polymerization of the polyester in the curing reaction that produces the solidified cement; curing of the Gerhart composition does not involve a reaction of the calcium salts and ceramics. Moreover, the calcium salts and ceramics do not contribute to a conversion

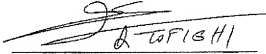
of the Gerhart composition into a PCA calcium phosphate, as occurs in the composition of present claims 45, 46, 58, 59, 73, and 75-77. Instead, according to Gerhart's description of the process, after curing, the calcium salts and the ceramics of the Gerhart composition remain in their original forms. The calcium salts are eluted from the polyester matrix by body fluids, which creates small voids or cavities in the polymer matrix, the ceramics are wholly or partially resorbed over time, and the polyester matrix is degraded *in vivo* into its component polymers (see col. 2, lines 49-56). Thus, in contrast to the composition of present claims 45, 46, 58, 59, 73, and 75-77, the Gerhart composition does not harden as a result of the reaction of a calcium phosphate and does not convert upon hardening into a PCA calcium phosphate.

7. In addition, the Gerhart composition cures in a mildly exothermic reaction (col. 4, lines 19-25, and col. 8, lines 30-32). It is the polymerization of the polyester with the chemical cross-linking agent that generates heat in a mildly exothermic reaction; the calcium salts and ceramics in the Gerhart composition, according to Gerhart, do not contribute to the curing reaction. Thus, the Gerhart composition cures to a solidified cement in a mildly exothermic chemical polymerization reaction whereas, in contrast, the composition of present claims 45, 46, 58, 59, 73, and 75-77 hardens in a distinctly different reaction that involves the conversion of a calcium phosphate to a PCA calcium phosphate in an endothermic reaction.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: December 15, 2009

  
Aliassghar N. Tofghi, Ph.D.